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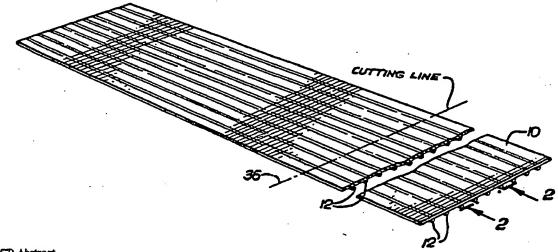
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**Published** 

With international search report. With amended claims.

(54) Title: ALLERGY SCREENING SYSTEM AND METHOD OF MAKING AND USING SAME



(57) Abstract

For use in allergy screening, a plurality of filaments (12) coated with different allergens and arranged in a predetermined spaced relationship on a support (10) to provide coincident measurement in a liquid specimen of IgE class antibodies specific for the allergens. The filaments (12) are preferably cotton threads that can covalently bind the allergens through cyanogen bromide induced linkages and the support (10), which can be cut away to reduce background, is preferably composed of a plastic or other water insoluble material, permitting inexpensive and relatively simple manufacturing. After IgE class antibodies present in a liquid sample have reacted with the allergens coated on the filaments (12), they are detected with second antibodies labeled with radioactive, fluorescent or enzymatic tracers. By using a high energy radioactive tracer, such as I125, autoradiographic techniques with phosphor screen enhancement allow for diagnostic analysis by densitometers or even the unaided human eye.

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## ALLERGY SCREENING SYSTEM AND METHOD OF MAKING AND USING SAME

## BACKGROUND OF THE INVENTION

This invention relates to binding assays for use in diagnostic analysis of liquid specimens and, more particularly, to a diagnostic system capable of detecting the presence of IgE class antibodies for allergy screening.

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One characteristic of mammals and other highly developed animals is the ability to protect themselves against the veritable onslaught of invading organisms and foreign material encountered on a constant or periodic basis. The protection originates in the initiation by the organism or foreign material of an immunogenic response in the animal. An important aspect of this immunogenic response is the production of immunoglobulins, so-called antibodies, against antigenic sites on the organisms or foreign material.

For reasons not yet completely understood, certain antigenic materials, known as allergens, often induce a hypersensitive response in human beings. This hypersensitivity, or allergy, can manifest itself in a number of readily identifiable symptoms, notably, hay fever, asthma, eczema, hives and localized swelling.

Traditionally, diagnostic analysis for the presence of this hypersensitivity in patients was accomplished with skin tests or provocation tests. In provocation tests the patient inhales the suspected allergen in aerosol form, whereas skin tests require applying the



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allergen to the patient's skin. Both tests necessitate monitoring the patient for evidence of allergic symptoms and require significant amounts of trained personnel time for proper evaluation. Moreover, in some cases exposure to the allergen can induce a strong allergic response, resulting in unnecessary discomfort, or even harm, to the patient.

As a result of discovery that a class of immunoglobulins, specifically IgE class antibodies, were in large part responsible for the allergic response, diagnosticians developed in vitro tests for IgE class antibodies utilizing standard radioimmunoassay techniques on serum. By way of example, several types of such tests can be found in U.S. Patent Nos. 3,877,307 and 4,243,651.

Successful research was also accomplished with respect to techniques for the screening of different IgE class antibodies, and by way of example, such techniques can be found in U.S. Patent Nos. 3,941,876 and 4,031,197. Basically, the techniques described in these patents include coating an elongated cellulosic body (e.g., a strip of paper) with separate identified allergens to form bands or islands, which are separated from one another by allergen-free areas. When this elongated body of cellulose material coated with the allergens is contacted with a test serum, serum IgE class antibodies specific for the coated allergens will attach to the appropriate places. After washing the cellulosic body and subsequently incubating it with labeled antibodies that are reactive with the attached IgE class antibodies, the bands and islands are analyzed for the presence of labeled antibodies. The information gleaned from the analysis provides an indication of the patient's allergic tendencies.

The methods and apparatus described in connection with the aforementioned screening patents are acceptable. However, the manufacture of the bands and islands on the cellulosic material is somewhat arduous

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and time consuming, typically requiring use of a jig for proper allergen coating. Also, for best results, all of the allergens should be coated on the cellulosic material at one time, mandating simultaneous allergen preparation. These constraints encumber the manufacturing process and limit the flexibility of the screening.

Accordingly, those concerned with the development and use of immunoassay techniques and related apparatus have recognized the desirability for further improvement in allergy screening systems. In particular, there has been a desire for improved and more economical manufacturing methods of devices useful for such screening. The present invention fulfills these needs.

#### SUMMARY OF THE INVENTION

The present invention provides a diagnostic system for use in the analysis of liquid specimens through binding assays, the system having a plurality of filaments coated with binding assay components from different assays for simultaneous contact with the liquid specimen and coincident measurement of the binding assay components. Moreover, the system construction of the present invention is relatively easy to manufacture, flexible, and inexpensive to make and use.

More specifically, a presently preferred embodiment of the invention is a diagnostic kit which includes a support having a plurality of cotton threads supported in a predetermined space relation for simultaneous contact with a liquid test sample. At least two of the threads are coated with allergen compositions specific to different IgE class antibodies for screening purposes. The threads are preferably made from cotton, a high molecular weight polysaccharide, so that the allergen can be covalently bound through cyanogen halide induced linkages. The preferred kit further includes second antibodies (antibodies reactive with the IgE

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class antibodies) that enable detection of IgE class antibodies bound to the threads. The second antibodies are preferably labeled with a radioactive tracer, such as  $\mathbf{I}^{125}$ , but may also be labeled with a fluorescent tracer, enzyme, enzyme substrate or coenzyme.

Another aspect of the invention is a method of detecting the presence of biological agents in a liquid specimen through the use of binding assays. This method includes the steps of incubating a liquid specimen with a plurality of filaments supported in a predetermined spaced relationship, at least two of the filaments being coated with a binding assay component from different assays; and analyzing the filaments to coincidentally determine the amount of multiple biological agents interacting with the binding assay components coated on the filament. The binding assay is preferably an immunoassay, and the analysis accomplished by autoradiography.

When screening for the presence of multiple allergen-specific IgE class antibodies in a liquid sample, the method includes the steps of: incubating the test sample with a plurality of filaments supported in a predetermined spaced relationship and coated with allergens specific to the IgE class antibodies in question; removing the filaments from the test sample; incubating the filaments with a solution containing labeled second antibodies against the IgE class antibodies; removing the filaments from the solution; and analyzing the filaments to determine the presence of the second antibodies.

If the second antibodies are radioactively labeled, such as with I<sup>125</sup>, the analysis can be accomplished with a gammacounter. An alternative analysis entails placing the filaments proximate to a film for exposure, and then analyzing the film's exposure by the unaided human eye, by a densitometer or by a scanning densitometer. A phosphor screen placed between the film

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and the filaments, often enhances film exposure.

When the second antibodies are labeled with a fluorescent tracer, the analysis can be accomplished with a fluorometer. Similarly, if the label is an enzyme or enzyme substrate, a spectrophotometer may be utilized.

A further aspect of the invention is a method of making an apparatus useful in the analysis of liquid specimens through binding assays. The method includes the steps of coating a filament with a component of a binding assay; and attaching a plurality of filaments in a spaced relationship to a support. At least two of the filaments are coated with components from different When the filaments are made of cotton binding assays. thread and the support of plastic, the support can be easily sliced into a plurality of elongated strips of a Further, the support can be parpredetermined size. tially cut away behind the filaments to reduce the background.

More specifically, a method of making a miniature apparatus for use in the simultaneous determination of the presence of multiple allergen-specific IgE class antibodies in a liquid test sample is provided. method includes the steps of coating a filament with an allergen composition specific to at least one of said IgE class antibodies; and attaching a plurality of these filaments to a support. At least two of the filaments attached to the support are coated with different allergen compositions. Again, the support can readily be sliced into a plurality of elongated strips of a predetermined size. The allergen composition can be composed of a mixture of related allergens, such as grass mix, mugwort mix, olive mix, ragweed mix, walnut mix, alternaria mix, dematiaceae mix or penicillium mix. more, the allergen composition can be composed of a defatted and extracted allergen.

It will be appreciated from the foregoing that the present invention represents a significant advance

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over previously available screening systems for allergy detection, principally because its manufacture is so simple and economical. Other aspects and advantages of the invention will become apparent from the following more detailed description taken in conjunction with the accompanying drawings.

### BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 is a perspective view of a system embodying the invention and showing a plurality of threads attached to an elongated support during manufacture:

FIG. 2 is an enlarged, fragmentary end view taken substantially along line 2-2 of Fig.1;

FIG. 3 is an exploded perspective view of the system embodying the invention, shown with an intensifying screen and film;

FIG. 4 is an end view of the system assembled with an intensifying screen and film;

FIG. 5 is a top plan view of the film partially exposed;

FIG. 6 is a perspective view of an alternative form of the system having a portion of the support cut away; and

FIG. 7 is a sectional view taken substantially along the line 7-7 in FIG. 6.

#### DESCRIPTION OF THE PREFERRED EMBODIMENT

Referring now to the drawings, and particularly to FIG. 1 and FIG. 3, there is shown a new and improved diagnostic system exhibiting features of the present invention. The system utilizes immunoassays for coincident measurement of multiple allergens in liquid specimens.

In accordance with the present invention, a

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support 10 is combined with a plurality of threads 12 supported in a predetermined spaced relation for simultaneous contact with a liquid test sample. The system construction of the present invention is relatively easy to manufacture, and is flexible and inexpensive to use.

The support 10 may be made from a plastic or from other water insoluble materials that are easily cut and available in strips. The threads 12 are preferably made from cotton, a high molecular weight polysaccharide, to permit allergen binding through cyanogen halide induced linkages. At least two of the threads 12 are coated with allergen compositions for reaction with different IgE class antibodies.

Each thread 12 is activated with cyanogen bromide as follows. A standard cotton basting thread, such as Brooks D-96N, cotton covered polyester or mercerized cotton, all available from Coats & Clark, Inc., Atlanta, Georgia, is wound onto a spindle, and about 3 grams placed in a beaker containing about 100 ml of fresh distilled water maintained at about 18°C. After adding a few drops of lN NaOH to the water, 5 grams of cyanogen bromide in 100ml distilled water are added, and the pH of the entire mixture monitored with a standard pH meter and the pH maintained at between about ten and eleven After about one hour, the thread is with lN NaOH. placed in about one liter of 0.005M NaHCO, , and the entire mixture is then poured over a sintered glass funnel. The thread held by the funnel is washed five times with 250ml of acetone and air drying for about one The activated threads are stored with a hour in a hood. dessicant in a petri dish covered with filter paper for two days or more at a temperature of about 4°C prior to coupling.

A wide variety of allergens can be bound to the activated threads, and by way of example, the following list contains a few of the preferred. The list contains

both the common and scientific names, along with the family for possible information on cross-reactivity.

#### Allergen

Birch (Betula alba) FAMILY: Alder

- Cat (1:10 environment bulk cat hair in 50% glycerol)
  Cockleburr, spiny (Xanthium spinosm) FAMILY: Compositae
  Curly dock (Runnex crispus) FAMILY: Polygonoceae
  English plantain (Plantago lanceolata) FAMILY: Plantaginaceae
- 10 False Ragweed (<u>Franseria acanthicarpa</u>) FAMILY: Compositae.

  Grass Mix:
  - a. Annual blue grass (Poa annua)
  - Bermuda grass (Cynodon dactylon)
  - c. English rye Grass (Lolium perenne)
- 15 d. Pescue, tall meadow grass (Pestuca elation)
  - e. Kentucky blue grass (Poa pratensis)
  - f. Orchard grass (Dactylis glomerata)
  - g. Redtop (Agrostis alba)
  - h. Salt grass (Distichlis spicata)
- i. Sweet vernal grass (Anthoxanthum odoratum)
  - j. Timothy (Phleum pratense)

House dust (2,000pnu/ml Albay A.P., bulk in 50% glycerol) Household insects

Juniper, western (Juniperus occidentalis)

25 Lambs quarter (Chenopodium album) FAMILY: Chenopod Live Oak (Quercus agrifolia)

Mite (1:100 mite bulk in 50% glycerin)

Dermatophagoides farinae

Mugwort mix FAMILY: Compositae

- 30 a. Artemesia campestris Pacifica
  - b. Calif. Mugwort (Artemesia vulgaris heterophylla)
  - c. Coast sage (Artemesia Californica)
  - d. Giant sagebrush (Artemesia tridentata)
  - e. Sand sagebrush (Artemesia filifolia)



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- f. Western sage (Artemesia suksdorfii)
  Mustard (brassica) FAMILY: Cruciferaeace
  Olive mix
  - a. Ash, Oregana (Fraxinus Oregana)
  - b. Olive, (Olea Europia)
  - c. Privet (Ligustrum vulgare)

Pickleweed (Salicornia ambigua) FAMILY: Chenopod
Pigweed, Careless weed (Amaranthus palmeri) FAMILY:
Amarantacea

- 10 Ragweed: mix FAMILY: Compositae
  - a. Short or common Ragweed (Ambrosia Elatior)
- b. Western Ragweed (Ambrosia psilostachla)
  Russian thistle (Salsola kali) FAMILY: Chenopod
  Sheep sorrel (Rumex acetosella) FAMILY: Polygoneace
  Spearscale (Atriplex patula) FAMILY: Chenopod
  Walnut mix:
  - a. California black (Juglans Calif.)
  - b. English walnut (Juglans regia)

Aspergillus

- 20 Alternaria Mix
  - a. Alternaria
  - b. Helminthosporium
  - c. Hormodendrum

Dematiaceae Mix

25 Dog hair and dander Monilia albicans Penicillium Mix

Many of the allergens may be purchased from Sharp & Sharp, Everett, Washington or as extracts from Hollister Steir, Spokane, Washington. Alternatively, they may be isolated utilizing techniques well known in the art. Generally, if not available as an extract, the allergens must be defatted and extracted into a aqueous solution prior to final binding to the threads.

By way of example, for defatting and extracting pollen, 3mls of diethylether are added to one gram of pollen powder. The preliminary extraction proceeds for

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about one hour, after which the ether is removed with an aspirator. This is repeated at least two times, and the defatted material allowed to dry overnight. About one gram of the defatted allergen is placed in 10mls of 0.1M phosphate buffer, pH 7.5, containing 0.9 wt. % NaCl and 0.1 wt. % NaN<sub>3</sub>. This solution is sonicated for about two minutes to properly suspend the allergen in the buffer, stored in a cold room for about 24 hours, and then sediment removed by centrifugation for about one hour. The supernatent is poured through a paper filter and a milipore filter of about 0.45 microns. If desired, the supernatent can be assayed for protein concentration by the well known Lowry method. Similarly, the amount of allergen present can be ascertained by standard radioimmunoassay techniques.

For coupling the allergens to activated threads, each allergen is first serially diluted in 0.1M Na<sub>2</sub>PO<sub>4</sub> buffer, pH 7.5, with 0.9 wt. % NaCl and 0.1 wt. % NaN<sub>3</sub> (dilution buffer), to concentrations ranging from about 1 to 10mg/ml. About 10mg of activated threads are added to 1ml of each dilution and gently rocked for about 24 hours at 4°C. The allergen dilution is then removed by aspiration and the threads washed two times with 0.1M NaHCO<sub>3</sub>. Thereafter, the threads are mixed with 1ml of 0.05M ethanolamine in 0.1M NaHCO<sub>3</sub>. After incubating for about 3 hours, the ethanolamine is removed by aspiration and the threads washed repeatedly: two times each with 0.5M NaHCO<sub>3</sub>; 0.1M CH<sub>3</sub>COONa, pH 4.0; and the dilution buffer with 0.2% human serum albumin.

To determine an optimal bulk coupling concentration for the allergen, a sample test utilizing a pool of positive sera (i.e., sera containing IgE class antibodies reactive with the specific allergen band) is run with the dilutions. About a 2.5cm length of a coated thread is added to a well with about 50ul of the pooled sera, and the well placed in a humid chamber containing H<sub>2</sub>O with 0.1 wt. % NaN<sub>3</sub>. After incubating for about



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eighteen to twenty-four hours, the liquid is aspirated off and the thread washed five times with the dilution buffer.

The thread is then incubated in the chamber, for about eighteen to twenty-four hours with a small volume, preferably about 50ul, of radioactively labeled second antibodies that are reactive with human IgE class antibodies. As is well known, suitable second antibodies can be obtained from the sera of goats or rabbits injected with human IgE, or from monoclonal sources, such as murine IgE available from Hybritech, Inc., La Jolla, California. The second antibodies are labeled with I<sup>125</sup> by traditional iodination techniques, such as described in Hunter and Greenwood, Nature 194: 495 (1962) and, if necessary, purified according to processes well known in the art.

After the incubation, the second antibody solution is aspirated off. The thread is again washed with five volumes of the dilution buffer, and then counted in a conventional gamma counter to quantify its radioactivity. The lowest serial dilution having a count level approximately equal to the maximum count level obtained from the serial dilutions is the optimal coupling concentration.

By way of example, the following list indicates a number of presently preferred coupling concentrations.

### ALLERGEN COUPLING CONCENTRATIONS

	Allergen	Concentration (mg/ml)
	Birch	2.0
30	Cat	0.05
	. Cockleburr	6.5
	Curly dock	5.3
	English plantain	2.0
	False Ragweed	5.2



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	Grass Mix	0.05
	House dust	3.0
	Household insects	3.7
	Juniper	4.9
5 .	Lambs quarter	3.0
	Live oak	0.5
	Mite	0.1
	Mugwort mix	1.0
	Mustard	1.0
10	Olive Mix	0.1
	Pickleweed	2.0
•	Pigweed	1.0
•	Ragweed Mix	5.4
	Russian thistle	1.0
15	Sheep sorrel	4.0
•	Spearscale	1.0
	Walnut	1.0
	Aspergillus	4.5
	Alternaria mix	2.6
20	Dematiaceae mix	3.9
	Dog hair and dander (IBI)	2.7
	Monilia albicans	2.6
	Penicillium mix	3.0

Once the allergens have been coated onto the threads 12, the threads are placed in a predetermined 25 spaced relationship, preferably parallel about 1.5 to 3.0mm apart, along a support 10, such as a plastic having a heat sensitive coating. By utilizing a hot knife to cut the support along a cutting line, which is generally indicated by numeral 36, the threads 12 can bind to 30 the support 10 as the heat sensitive coating melts. Thus, varying length strips with a number of threads, each coated with a different allergen, are readily prepared.

As shown in PIG. 3, a device 14 having a support 16 combined with the threads 18, all of which are

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coated with different allergens, is suitable for screening purposes. The device 14 is first placed in a liquid sample and incubated for a time sufficient to allow any IgE class antibodies present in the liquid sample to bind to the allergens on the threads. The device 14 is removed from the liquid sample, washed, and then incubated with a solution containing the previously described radioactively labeled second antibodies that are reactive with human IgE class antibodies. Thereafter, the device is removed from the radioactive second antibody solution, and the amount of radioactivity on the threads 18 determined.

As illustrated in the alternative embodiment of FIG. 6 and FIG. 7, a support 20 may have a plurality of slits 22 aligned along opposite edges of the support to hold the threads 13 in a transverse fashion. the support 20 may have interior portions cut away, indicated generally by the numeral 26, providing an open This allows improved area behind the threads 24. sensitivity due to the absence of a background. example, when the support 20 is incubated in a radioactive second antibody solution, radioactivity could be absorbed and retained by the support even after repeated By utilizing the cutaways 26 behind the washings. threads 24, any radioactivity absorbed by the support 20 would not significantly interfere with subsequent analysis of the threads.

In a preferred embodiment, the amount of radioactivity is determined autoradiographically. As illustrated in FIG. 3 and FIG. 4, the device 14 is placed proximate to a standard X-ray film 28, such as Kodak, Ortho H X-ray film, with the threads 18 facing the film. To promote exposure, a radio-absortive, photon emitting phosphorous screen 30, such as EK Lanex available from the Picker Corporation, or described in "X-Ray Exposure Reduction Using Rare-Earth Oxysulfide Intensifying Screens", Buchanan et al, Radiology 105: 185-90

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(1972), is then placed between the device 14 and film 28. Alternatively, two phosphor screens may sandwich the film 28 and device 14 (not shown). The assembly 32 is held in a dark room for a period of time sufficent to expose the film to any radioactivity on the threads, and then developed. When the radioactivity on a thread exceeds 20,000 cpm, an exposure time of one hour is acceptable. Similarly, for 5,000-20,000 cpm, an exposure time of eight hours is preferred, and for 1,000-5,000 cpm, 21 hours can be utilized. The length of exposure time will, of course, vary with the type of film, phosphor screen and other parameters.

FIG. 5 illustrates the film 28 having three exposure lines 34 from the exposure during positioning in the assembly 32. The lines 34 indicate that the liquid specimen contained IgE class antibodies specific for the allergen coated on each complementary thread 18.

From the foregoing, it will be appreciated that the diagnostic system of the present invention allows the coincident determination of a large number of allergens in a liquid specimen, thereby providing an effective allergy screening system. Further, the system is very economical, in that it is simple to manufacture and, additionally, is easy and inexpensive to analyze.

While a particular form of this invention has been illustrated and described, it will be apparent that various modifications may be made without departing from the spirit and scope of the invention.



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### CLAIMS

- 1. A diagnostic system for use in the diagnostic analysis of liquid specimens through binding assays, said diagnostic system comprising a plurality of filaments supported in a spaced relationship for simultaneous contact with said liquid specimen, at least two of said filaments being coated with a binding assay component from different assays for multiple, coincident measurement of said assay.
- 2. The diagnostic system of Claim 1 wherein the filament consists essentially of a polysaccharide.
- 3. The diagnostic system of Claim 1 wherein said liquid specimen is analyzed for multiple allergen-specific IgE class antibodies and wherein said bonding assay component comprises allergen compositions specific to different IgE class antibodies.
- 4. The diagnostic system of Claim 3 wherein each allergen composition is bound to a filament through a convalent bond.
- 5. The diagnostic system of Claim 4 wherein said convalent bond is formed with a cyanogen halide.
- 6. The diagnostic system of Claim 3 further comprising labelled antibodies reactive with said IgE for detection and measurement of IgE class antibodies bound to said thread.
- 7. A method of detecting the presence of biological agents in a liquid speciment through binding assays, said method comprising the steps of: incubating said liquid specimen with a plurality of filaments supported in a predetermined space relationship, at least two of said filaments being coated with a binding assay component from different assays; and analyzing said filaments to coincidently determine which of the biological agents interact with said binding assay components coated on said filament.
- 8. The method of Claim 7 or the diagnostic system of Claim 1 wherein said binding assays are immunoassays and wherein said binding assay component is an antigen.

- 9. A method of screening for the presence of multiple allergen-specific IgE class antibodies in a liquid test sample, said method comprising the steps of: incubating said test sample with a plurality of filaments supported on a support in a predetermined spaced relationship and coated with allergens specific to said IgE class antibodies; removing said filaments from said test sample; incubating said filaments with a solution containing labelled antibodies that are reactive with said IgE class antibodies; removing said filaments from said solution; and analyzing said filaments to determine the presence of said labelled antibodies; wherein at least two of said filaments are coated with different allergens.
- 10. The method of Claim 9 or the diagnostic system of Claim 6 wherein the labelled antibodies reactive with said IgE class antibodies are labelled with a

radioactive label, a fluorescent label, or an enzyme label.

- 11. The method of Claim 7 or Claim 9 wherein the analysis of the filament for the presence of labelled antibodies is accomplished by placing the filaments proximate to a film for exposing said film by said labelled antibodies.
- 12. A method for making an apparatus useful in the diagnostic analysis of liquid speciments through binding assays, said method comprising the steps of: coating a filament with a component of a binding assay; and attaching in a spaced relationship a plurality of filaments to a support; wherein at least two of said filaments are coated with components for different assays.
- 13. The method of Claim 12 wherein said liquid specimen is analyzed for multiple allergen-specific IgE class antibodies, said component of a binding assay comprises an allergen composition specific to at least one of said IgE class antibodies and said allergen AUREAN

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composition is convalently bound to said filament.



# AMENDED CLAIMS (received by the International Bureau on 14 December 1982 (14.12.82))

- 1. A diagnostic system for use in the diagnostic analysis of liquid specimens through binding assays, said diagnostic system comprising a plurality of filaments supported in a spaced relationship for simultaneous contact with said liquid specimen, at least two of said filaments being coated with a binding assay component from different assays for multiple, coincident measurement of said assay.
- 2. The diagnostic system of Claim 1 wherein the filament consists essentially of a polysaccharide.
- 3. The diagnostic system of Claim 1 wherein said liquid specimen is analyzed for multiple allergen-specific IgE class antibodies and wherein said binding assay component comprises allergen compositions specific to different IgE class antibodies.
- 4. The diagnostic system of Claim 3 wherein each allergen composition is bound to a filament through a covalent bond.
- 5. The diagnostic system of Claim 4 wherein said covalent bond is formed with a cyanogen halide.
- 6. The diagnostic system of Claim 3 further comprising labelled antibodies reactive with said IgE for detection and measurement of IgE class antibodies bound to said thread.
- 7. A method of detecting the presence of biological agents in a liquid specimen through binding assays, said method comprising the steps of: incubating said liquid specimen with a plurality of filaments supported in a predetermined spaced relationship, at least two of said filaments being coated with a binding assay component from different assays; and analyzing said filaments to coincidently determine which of the biological agents interact with said binding assay components coated on said filament.
- 8. The method of Claim 7 or the diagnostic system of Claim 1 wherein said binding assays are immunoassays and wherein said binding assay component is an antigen.

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- 9. A method of screening for the presence of multiple allergen-specific IgE class antibodies in a liquid test sample, said method comprising the steps of: incubating said test sample with a plurality of filaments supported on a support in a predetermined spaced relationship and coated with allergens specific to said IgE class antibodies; removing said filaments from said test sample; incubating said filaments with a solution containing labelled antibodies that are reactive with said IgE class antibodies; removing said filaments from said solution; and analyzing said filaments to determine the presence of said labelled antibodies; wherein at least two of said filaments are coated with different allergens.
- 10. The method of Claim 9 or the diagnostic system of Claim 6 wherein the labelled antibodies reactive with said IgE class antibodies are labelled with a

radioactive label, a fluorescent label, or an enzyme label.

- 11. The method of Claim 7 or Claim 9 wherein the analysis of the filament for the presence of labelled antibodies is accomplished by placing the filaments proximate to a film for exposing said film by said labelled antibodies.
- in the diagnostic analysis of liquid specimen through binding assays, said method comprising the steps of: coating a filament with a component of a binding assay; and attaching in a spaced relationship a plurality of filaments to a support; wherein at least two of said filaments are coated with components for different assays.
- 13. The method of Claim 12 wherein said liquid specimen is analyzed for multiple allergen-specific IgE class antibodies, said component of a binding assay comprises an allergen composition specific to at least one of said IgE class antibodies and said allergen BUREAU

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composition is covalently bound to said filament.



### **EDITORIAL NOTE**

The applicant failed to renumber the amended claims in accordance with Section 205 of the Administrative Instructions.

In the absence of any specific indication from the applicant as to the correspondence between original and amended claims, these claims are published as filed and as amended.

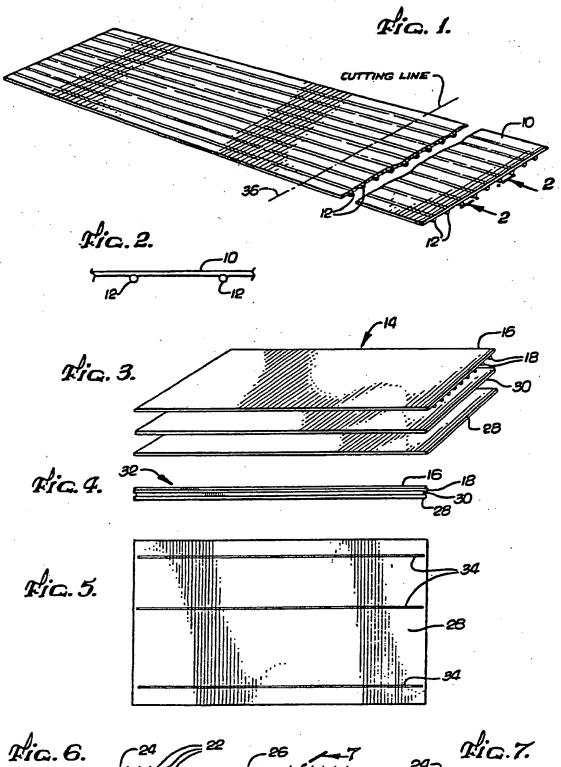


Fig. 6. 22 26 7 Ric.7.

20 Fig. 7 22 20 26 BUREAU

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#### INTERNATIONAL SEARCH REPORT

International Application No PCT/US82/0089

A US, A, 2,190,745 published 20 Feb 1940, Volumer.  A US, A, 2,788,339 published 31 Mar 1942, Volumer.  A US, A, 3,802,782 published 39 Apr 1974, Natelson.  A US, A, 3,802,782 published 03 Dec 1974, Wood et al.  A US, A, 3,941,876 published 20 Mar 1976, Marinkovich.  A US, A, 4,031,197 published 21 Jun 1977, Geiger.  A US, A, 4,034,601 published 21 Jun 1977, Geiger.  A US, A, 4,180,383 published 21 Jun 1977, Geiger.  A US, A, 4,219,530 published 21 Jun 1977, Geiger.  A US, A, 4,219,530 published 22 Dec 1979, Johnson.  A US, A, 4,219,530 published 22 Dec 1979, Johnson.  A US, A, 4,219,530 published 25 Dec 1979, Johnson.  A US, A, 4,219,530 published 25 Dec 1979, Johnson.  A US, A, 4,219,530 published 30 Jun 1980, Brennan.  A US, A, 4,270,548 published 30 Jun 1980, Brennan.  A US, A, 4,270,548 published 30 Jun 1980, Brennan.  A US, A, 4,270,548 published 30 Jun 1980, Brennan.  A US, A, 4,270,548 published 30 Jun 1980, Brennan.  A US, A, 4,270,548 published 30 Jun 1980, Brennan.  A US, A, 4,270,548 published 30 Jun 1980, Brennan.  A US, A, 4,270,548 published 30 Jun 1980, Brennan.  A US, A, 4,270,548 published 30 Jun 1980, Brennan.  A US, A, 4,270,548 published 30 Jun 1981, Brennan.  A US, A, 4,270,548 published 30 Jun 1980, Brennan.  A US, A, 4,270,548 published 30 Jun 1980, Brennan.  A US, A, 4,270,548 published 30 Jun 1981, Brennan.  A US, A, 4,270,548 published 30 Jun 1981, Brennan.  A US, A, 4,270,548 published 30 Jun 1981, Brennan.  A US, A, 4,270,548 published 30 Jun 1981, Brennan.  A US, A, 4,270,548 published 50 Jun 1981, Brennan.  A US, A, 4,270,548 published 50 Jun 1981, Brennan.  A US, A, 4,270,548 published 50 Jun 1981, Brennan.  Brennan.				n att alama10				/0302/00093	
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Natelson.  A US, A, 3,802,782 published 09 Apr 1974, Natelson.  A US, A, 3,852,035 published 03 Dec 1974, Wood et al.  A US, A, 3,941,876 published 02 Mar 1976, Marinkovich.  A US, A, 4,031,197 published 21 Jun 1977, Marinkovich.  A US, A, 4,034,601 published 12 Jul 1977, Geiger.  A US, A, 4,180,383 published 25 Dec 1979, Johnson.  A US, A, 4,219,530 published 03 Jun 1980, Brennan.  A US, A, 4,219,530 published 03 Jun 1980, Kopp et al.  A US, A, 4,270,548 published 02 Jun 1981, Brennan.  * Special categories of clade documenta: 19  "A" document defining the general state of the art which is not considered to be of particular research.  "Special categories of clade documenta: 19  "A document which may throw doubts on priority claim(a) or other special reason (as specified)  "O" document make the priority throw doubts on priority claim(a) or other special reason (as specified)  "O" document published prior to the international filing date but later than the priority date claimed  "O" document published prior to the international filing date but later than the priority date claimed  "O" document published prior to the international filing date but later than the priority date claimed  "O" document published prior to the international filing date but later than the priority date claimed  "O" document published prior to the international filing date but later than the priority date claimed  "O" document published prior to the international filing date but later than the priority date claimed  "O" document published prior to the international filing date but later than the priority date claimed  "O" document published prior to the international filing date but later than the priority date claimed  "O" document published prior to the international filing date but later than the priority date claimed  "O" document published prior to the international filing date but later than the priority date claimed  "O" document published prior to the international filing date but later than the priority date claimed  "O" document		Vollme	7° -				-		
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Wood et al.  US, A, 3,941,876 published 02 Mar 1976, Marinkovich.  A US, A, 4,031,197 published 21 Jun 1977, Marinkovich.  A US, A, 4,034,601 published 12 Jul 1977, Geiger.  A US, A, 4,180,383 published 25 Dec 1979, Johnson.  A US, A, 4,205,689 published 03 Jun 1980, Brennan.  A US, A, 4,219,530 published 26 Aug 1980, Kopp et al.  A US, A, 4,270,548 published 02 Jun 1981, Brennan.  *Special categories of cited documents: 19 "A" document defining the general state of the art which is not considered to be of particular relevance. "E" earlier document which may throw doubts on priority claim(s) or "T" document which may throw doubts on priority claim(s) or "T" document which may throw doubts on priority claim(s) or "T" document which may throw doubts on priority claim(s) or "T" document which may throw doubts on priority claim(s) or "T" document which may throw doubts on priority claim(s) or "T" document which may throw doubts on priority claim(s) or "T" document which may throw doubts on priority claim(s) or other special reason (as specified)  "O" document expectation or other special reason (as specified) "O" document published prior to the international filing date but later than the priority date claimed  "A" document published prior to the international filing date but later than the priority date claimed  """ document published prior to the international filing date but later than the priority date claimed  """ document is combined with one or more other such decuments, such combination being obvious to a person shilled in the art.  """ document is combined with one or more other such decuments, such combination being obvious to a person shilled in the art.  """ document is combined with one or more other such decuments, such combination being obvious to a person shilled in the art.  """ document is combined with one or more other such decuments, such combination being obvious to a person shilled in the art.  """ document member of the same petent family  IN. CERTIFICATION  Date of Mailing of this internati				•		-		1-13	
Wood et al.  US, A, 3,941,876 published 02 Mar 1976, Marinkovich.  A US, A, 4,031,197 published 21 Jun 1977, Marinkovich.  A US, A, 4,034,601 published 12 Jul 1977, Geiger.  A US, A, 4,180,383 published 25 Dec 1979, Johnson.  A US, A, 4,205,689 published 03 Jun 1980, Brennan.  A US, A, 4,219,530 published 26 Aug 1980, Kopp et al.  A US, A, 4,270,548 published 02 Jun 1981, Brennan.  *Special categories of cited documents: 19 "A" document defining the general state of the art which is not considered to be of particular relevance. "E" earlier document which may throw doubts on priority claim(s) or "T" document which may throw doubts on priority claim(s) or "T" document which may throw doubts on priority claim(s) or "T" document which may throw doubts on priority claim(s) or "T" document which may throw doubts on priority claim(s) or "T" document which may throw doubts on priority claim(s) or "T" document which may throw doubts on priority claim(s) or "T" document which may throw doubts on priority claim(s) or other special reason (as specified)  "O" document expectation or other special reason (as specified) "O" document published prior to the international filing date but later than the priority date claimed  "A" document published prior to the international filing date but later than the priority date claimed  """ document published prior to the international filing date but later than the priority date claimed  """ document is combined with one or more other such decuments, such combination being obvious to a person shilled in the art.  """ document is combined with one or more other such decuments, such combination being obvious to a person shilled in the art.  """ document is combined with one or more other such decuments, such combination being obvious to a person shilled in the art.  """ document is combined with one or more other such decuments, such combination being obvious to a person shilled in the art.  """ document member of the same petent family  IN. CERTIFICATION  Date of Mailing of this internati	A			publishe	d 03	Dec	1974,	· ·	
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